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Original Article

Brugada syndrome in the presence of coronary artery disease

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ABSTRACT

Background: Brugada-type ECG changes have been described in association with various cardiac disease states including electrolyte abnormalities, myocardial pathologies, and mechanical cardiac abnormalities as well as drug therapies with particular medications. Such potential confounding factors make it difficult to diagnose Brugada syndrome on the basis of standard guidelines.
Methods: To investigate the incidence of significant coronary artery disease in patients with Brugada-type ECG, coronary angiography was performed in 55 patients with Brugada-type ECGs.
Results: Five of the 55 patients (9%) had significant coronary artery stenosis, and 3 out of these 5 were asymptomatic. Patients with coronary artery disease were older than in those without coronary artery disease (59.4 ± 7.2 years vs. 49.0 ± 13.8 years, $P=0.03$). An electrophysiological study was performed in 4 of the 5 patients, and ventricular fibrillation was induced in all 4.
Conclusions: We conclude that patients with Brugada-type ECGs should be evaluated for coronary artery disease, and this is especially important for patients in whom age could be a risk factor for the disease.

1. Introduction

Brugada syndrome is characterized by ST-segment elevation in the right precordial leads and sudden cardiac death (SCD) [1]. In general, the mean age of victims of SCD is approximately 40 years [2]. Brugada syndrome is believed to account for 4–12% of all cardiac deaths and at least 20% of deaths in patients with a structurally normal heart [2]. Thus, the timely diagnosis of Brugada syndrome is clinically imperative. However, myocardial ischemia can cause right ventricular ST-segment elevation similar to the Brugada ECG pattern [3–7], and the coexistence of Brugada syndrome with vasospastic angina has been reported [8–12]. In addition, Brugada syndrome has been reported to associate with individual cases of significant coronary artery stenosis [13–17]. Thus, Brugada syndrome cannot be diagnosed simply on the basis of standard guidelines if such potential confounding factors are present [2,7]. The present retrospective study was undertaken to evaluate the coexistence of Brugada syndrome and coronary artery disease in a single center.

2. Materials and methods

2.1. Patients

The subjects in this study included 55 consecutive patients with a spontaneous or drug-induced (pilsicainide 1 mg/kg) Brugada type 1 ECG pattern. The ECG diagnosis of Brugada syndrome was based on recommendations issued at the second consensus conference [2]. No patients with true right bundle branch block were included in the study. All 55 patients underwent transthoracic echocardiography, cardiac catheterization, coronary angiography, and left and right ventricular angiography, while 54 of the 55 patients also underwent an electrophysiological study. All study protocols (coronary angiography including coronary spasm induction by intracoronary administration of acetylcholine and electrophysiological studies) were approved by the Clinical Research Committee of Nihon University Hospital, and written informed consent was obtained from all patients.

Laboratory tests were performed at the outpatient clinic to exclude electrolyte or metabolic disturbances. The following clinical data were obtained from each patient's record: sex, age, symptom(s), family history of SCD (<45 years of age), ECG pattern (type 1, type 2, or type 3 before drug challenge test), and whether an implantable cardioverter-defibrillator (ICD)

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was indicated. Patients with a history of syncope, presyncope, or aborted SCD were considered symptomatic. Those with established neurally mediated syncope were not considered symptomatic. Screening for mutations in the SCN5A gene was performed in 37 individuals after approval of the internal review board of the Nihon University School of Medicine and Nihon University Hospital.

2.2. Signal-averaged electrocardiogram

A ventricular signal-averaged electrocardiogram (ART 1200 EPX signal-averaged ECG apparatus, Arrhythmia Research Technology Inc., Austin, TX, USA; noise level < 0.3 μV, bidirectional 4-pole Butterworth high pass filter setting of 40 Hz) was recorded in 52 patients. A positive late potential is defined at our institution as the root mean square voltage of the last 40 ms < 20 μV [18].

2.3. Electrophysiological study

A comprehensive electrophysiological study was performed on 54 patients in a fasting, drug-free, and non-sedated state. In patients who underwent coronary artery stent implantation, a programmed ventricular stimulation (PVS) study was performed for 1 month. After access to the right femoral vein was obtained at 4 sites, 1 quadripolar catheter (Biosense-Webster, Diamond Bar, CA, USA) was positioned at the right atrial appendage, 1 octapolar catheter (Biosense-Webster) was positioned at the His bundle electrogram recording site, and 2 steerable quadripolar catheters (6F) with an interelectrode distance of 2-5-2 mm (Biosense-Webster) were positioned in the right ventricular apex and outflow tract. The endocardial potentials were filtered to recording frequencies of 30–500 Hz and recorded on a BARD computer system (BARD Lab Pro, BARD Electrophysiology, Lowell, MA, USA). Programmed electrical stimulation from the right ventricular apex and right ventricular outflow tract was performed at strength of twice the diastolic threshold, and a 2-ms pulse was applied with a pulse generator (BD-02, Fukuda Denshi Co., Tokyo, Japan). An S_1-S_2 interval was applied after 8 beats of drive pacing (S_1) at basic cycle lengths of 600 ms and 400 ms. The S_1-S_2 interval was decreased in 10-ms steps until the effective refractory period of the right ventricle was reached. When ventricular fibrillation (VF) that lasted > 5 s and required direct current (DC) shock was not induced with a single premature beat, 3 extrastimuli (S_2 until the effective refractory period was reached, S_3 and S_4 to 180 ms) were delivered.

2.4. Follow-up

In general, patients were followed up at 4- to 5-month intervals in our outpatient clinic. Each examination included an assessment of subjective symptoms, 12-lead ECG, and device interrogation if necessary in the event of symptom onset or device discharge. The follow-up period ranged from 6 to 194 months (mean, 81.0 ± 47.5 months; median, 77 months).

2.5. Statistical analysis

Continuous clinical and electrophysiological values are shown as mean ± SD. Between-group differences in these values were analyzed by the Mann–Whitney U test. Categorical data were analyzed by Fisher's exact probability test. A P value of < 0.05 was considered statistically significant. StatView 5.0 software (SAS Institute, Cary, NC, USA) was used for analysis.

3. Results

The male/female sex ratio in the study group was 53/2, and the mean age was 50.4 ± 13.8 years (range, 24–79 years). Brugada syndrome ECG patterns were spontaneous type 1 ($n=31$) and drug-induced type 1 ($n=24$; type 2 = 14, type 3 = 10). The clinical, genetic, electrocardiographic, and electrophysiological characteristics of the study patients are shown in Table 1. Eleven patients were symptomatic (3 with history of syncope, 2 with presyncope, and 6 with aborted SCD), and 5 patients had a positive family history of SCD. An SCN5A gene mutation was found in 2 patients (5.4%). The left ventriculogram was normal with an ejection fraction of 69.2% ± 9.0% (55–89%) in 55 patients who had undergone left ventricular angiography. The coronary angiogram, although normal in 49 patients, revealed significant coronary artery disease in 5 patients. Risk factors in patients with coronary artery disease are listed in Table 2. Patients with coronary artery disease were older than those without coronary artery disease (59.4 ± 7.2 years vs. 49.0 ± 13.8 years, $P=0.03$) (Table 1). Two of the 5 patients (Patients 2 and 4) exhibited symptoms related to coronary artery disease. PVS was performed in 50 patients without significant coronary artery stenosis and in 4 of the 5 patients with coronary artery disease, which induced VF/

Table 1
Clinical, genetic, electrocardiographic, and electrophysiological characteristics of all patients and patients with and without Coronary Artery Disease (CAD).

	Total patients $N=55$	Patients with CAD ($n=5$)	Patients without CAD ($n=50$)	P value
Number of males	53	5 (100%)	48 (96.0%)	0.86
Age (years)	50.4 ± 13.8 (24–79)	59.4 ± 7.2	49.0 ± 13.8	0.03
Symptomatic	10	1 (20.0%)	9 (18.0%)	0.83
Family history of SCD	7	0	7 (14.0%)	0.65
Spontaneous type 1 ECG pattern	31	1 (20.0%)	30 (60.0%)	0.11
Late potentials	27	2 (40.0%)	25 (50.0%)	0.64
SCN5A gene mutation	2	0	2 (4.0%)	0.86
PR interval (ms)	172.1 ± 24.9	170.8 ± 15.2	172.2 ± 25.8	0.99
QTc (ms)	413.3 ± 22.8	401.2 ± 14.1	414.5 ± 23.3	0.23
QRS duration (ms)	106.7 ± 17.6	102.4 ± 16.1	107.2 ± 17.8	0.84
EPS	54	4	50	0.87
AH (ms)	101.5 ± 20.0	126.3 ± 26.8	99.5 ± 18.3	0.03
HV (ms)	47.8 ± 10.4	37.0 ± 2.2	48.7 ± 10.3	0.19
Inducible VF/PVT upon EPS	49/55 (89.1%)	4/4 (100%)	45/50 (90.0%)	0.17
ICD implantation	19	1	18	0.17
Follow-up (months)	81.0 ± 47.5	67.1 ± 50.6	80.2 ± 49.4	0.22
Arrhythmic event during follow-up	1	0	1 (1.5%)	> 0.99

The number of patients is shown unless otherwise indicated. CAD, coronary artery disease; SCD, sudden cardiac death; EPS, electrophysiological study; VF, ventricular fibrillation; PVT, polymorphic ventricular tachycardia; ICD, implantable cardioverter defibrillator.

polymorphic ventricular tachycardia (PVT) in 45 of the 50 patients (90%) without coronary artery disease and in the 4 patients with coronary artery disease (Table 2). Details regarding the electrophysiological data and the coronary angiogram are provided in Table 3. An ICD was implanted in 19 patients who had inducible PVT/VF and desired an ICD implant (38.8%). Two representative cases of coronary artery disease are described below.

3.1. Patient 1

This patient was a 71-year-old man who had undergone right artificial hip replacement surgery for arthritis deformans at our orthopedics department. After his surgery, we observed frequent ventricular premature beats on the ECG monitor, and we noted an incomplete right bundle branch block and STT elevation (type 2 Brugada ECG) on the 12-lead ECG (Fig. 1, left and middle). A pilsicainide challenge test was performed, and the ECG changed to a type 1 pattern in leads V_1 and V_2 (Fig. 1, right). The coronary angiogram (CAG) revealed 90% stenosis of the proximal left anterior descending coronary artery (LAD) (segment ♯7), 99% stenosis of the middle portion of the right coronary artery (RCA) (segment ♯3), and total occlusion of the posterior descending (PD) coronary artery (Fig. 2 upper panel). A stent was implanted in LAD segment ♯7. Programmed ventricular stimulation was performed 1 month later, and VF was induced by double extrastimuli from the right ventricular apex (S_1: 400 ms, S_2: 230 ms, S_3: 200 ms). Thus, an ICD was implanted Table 3.

Table 2
Risk factors for Brugada syndrome patients with coronary artery disease.

Patient	Age (years)	Sex	FH	BMI	HT	Dyslipidemia	DM	Brinkman Index
1	71	male	−	22.0	+	−	+	1000
2	54	male	−	17.6	−	−	−	560
3	58	male	−	25.8	−	+	+	0
4	53	male	−	23.9	+	+	+	0
5	61	male	−	19.7	−	+	−	0

FH, family history of the coronary heart disease; BMI, body mass index; HT, hypertension; DM, diabetes mellitus; Brinkman Index, number of cigarettes smoked per day × number of years of smoking.

3.2. Patient 2

This patient was a 54-year-old man who had anterior chest discomfort and visited another hospital. His 12-lead ECG showed an incomplete right branch block and ST elevation (type 2 Brugada ECG) (Fig. 3, left), and he was referred to our hospital. An emergency CAG indicated 90% stenosis of the second diagonal branch (segment ♯10) of the LAD. No percutaneous intervention was performed. PVS was performed and VF was induced by double extrastimuli from the right ventricular outflow tract (S_1: 600 ms, S_2: 230 ms, S_3: 200 ms).

3.3. Patient 3

This patient was a 53-year-old man who was hospitalized at the Neurology Division due to cerebral infarction. Upon his admission, a 12-lead ECG showed an incomplete right branch block and ST elevation (type 2 Brugada ECG) (Fig. 3, middle). A CAG and a PVS were performed prior to discharge. The CAG revealed total occlusion of the left circumflex coronary artery branch (♯13). VF was induced by double extrastimuli from the right ventricular apex (S_1: 400 ms, S_2: 210 ms, S_3: 190 ms).

3.4. Patient 4

This patient was a 58-year-old man who had anterior chest pain and visited his family doctor. A 12-lead ECG showed an incomplete right branch block and STT elevation (type 1 Brugada ECG) (Fig. 3, right). He was referred to our hospital because acute coronary syndrome was suspected. An emergency CAG revealed 90% stenosis of the LAD (segment ♯7), 90% stenosis of LCX segment ♯13, and 50% stenosis of segment ♯14. A coronary stent was implanted in LAD segment ♯7. PVS was performed 3 months later, and VF was induced by double extrastimuli from the right ventricular outflow tract (S_1: 400 ms, S_2: 210 ms, S_3: 200 ms).

3.5. Patient 5

This patient was a 61-year-old man who underwent laryngectomy for laryngeal cancer in our otolaryngology department.

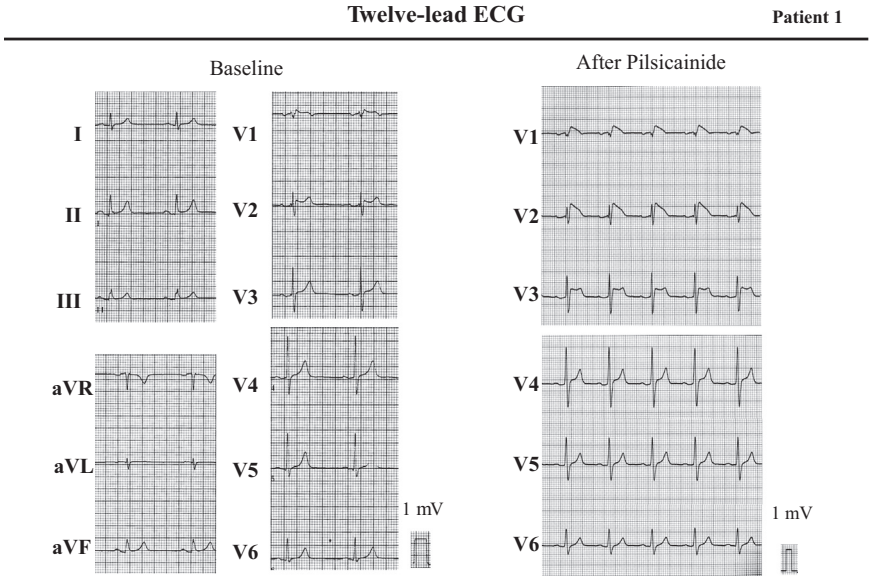

Fig. 1. Twelve-lead ECG from Patient 1. Note the type 2 Brugada pattern in the right precordial leads (left and middle panels), which was altered to a type 1 ECG by intravenous administration of 1 mg/kg pilsicainide (right panel).

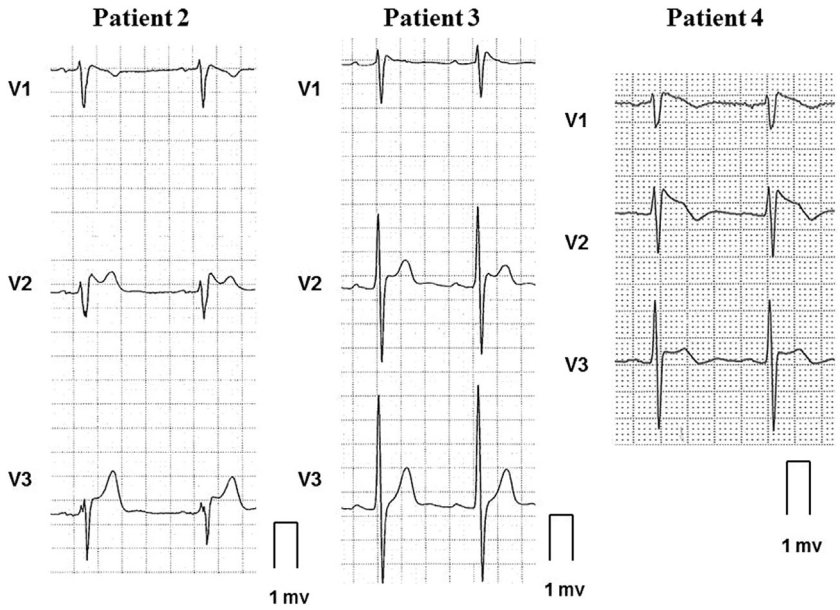

Fig. 2. Right precordial lead ECGs from patients 2–4. Note that patients 2 and 3 showed a type 2 Brugada ECG, and patient 4 showed a type 1 Brugada ECG.

Table 3
Clinical characteristics of Brugada syndrome patients with coronary artery disease.

Patient	Age (years)	Sex	ECG	FH	LP	VF induction (ms)	CAG	PCI ICD
1	71	Male	Type 2	−	−	A: 400/230/200	4PD: total RCA #3: 99%, LAD #7: 90%	+ +
2	54	Male	Type 2	−	+	O: 600/230/200	LAD D2: 90%	− −
3	58	Male	Type 2	−	+	A: 400/210/190	CX #13: total	− −
4	53	Male	Type 1	−	−	O: 400/210/200	LAD #7: 90% LCX #13: 90% LCX #14: 50%	+ −
5	61	Male	Type 3	−	−	Not performed	LAD #7: 90%	+ −

ECG, Brugada type ECG; FH, family history of sudden cardiac death; LP, late potentials; VF, ventricular fibrillation; CAG, coronary angiogram; PCI, percutaneous coronary intervention; ICD, implantable cardioverter defibrillator; A, right ventricular apex; O, right ventricular outflow tract; LAD, left anterior descending coronary artery; RCA, right coronary artery; CX, left circumflex coronary artery; PD, posterior descending coronary artery.

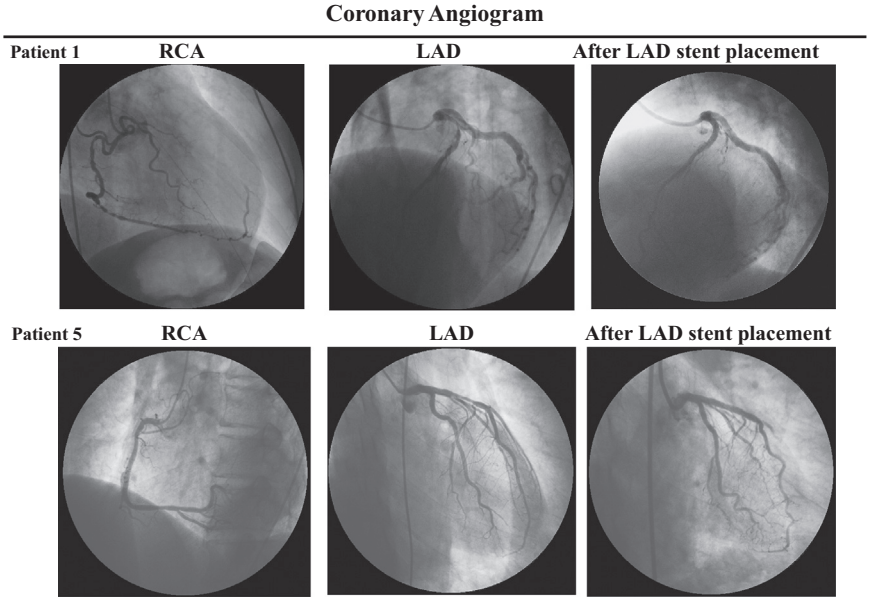

Fig. 3. Coronary angiogram obtained from Patient 1 (upper panels). Note the 90% stenosis of the proximal portion of the left descending coronary artery (segment #7), the 99% stenosis of the middle portion of the right coronary artery (segment #3), and the total occlusion of the posterior descending coronary artery. Coronary angiogram obtained from Patient 5 (lower panels). Note the 90% stenosis of the proximal portion of the left anterior descending coronary artery (segment #7).

One year later, he developed stenosis of the tracheostomy fistula, and he was admitted to our hospital for dilatation of the tracheostomy fistula. Upon his admission, a 12-lead ECG showed an incomplete right bundle branch block and J point elevation in

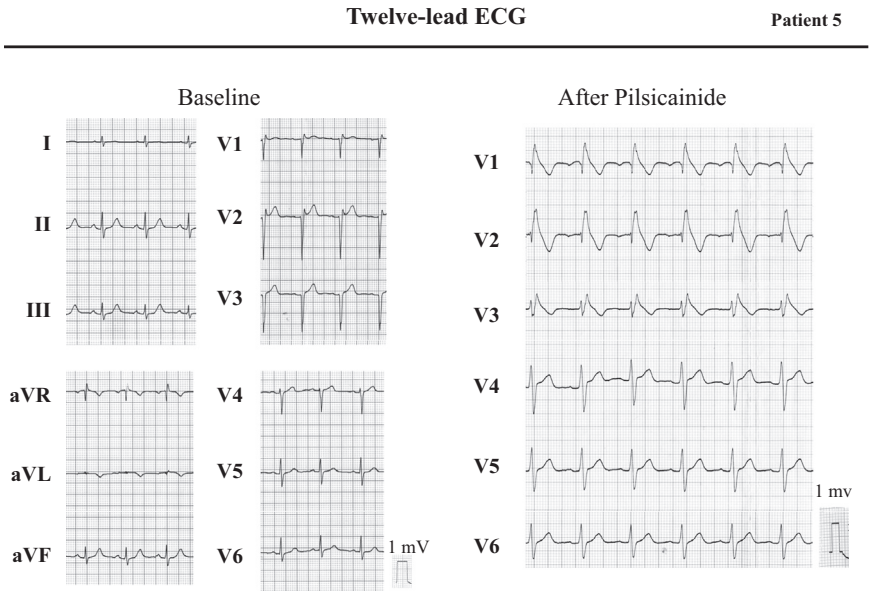

Fig. 4. Twelve-lead ECG from Patient 5. Note the type 3 Brugada pattern in the right precordial leads (left and middle panels), which was altered to a type 1 ECG by intravenous administration of 1 mg/kg pilsicainide (right panel).

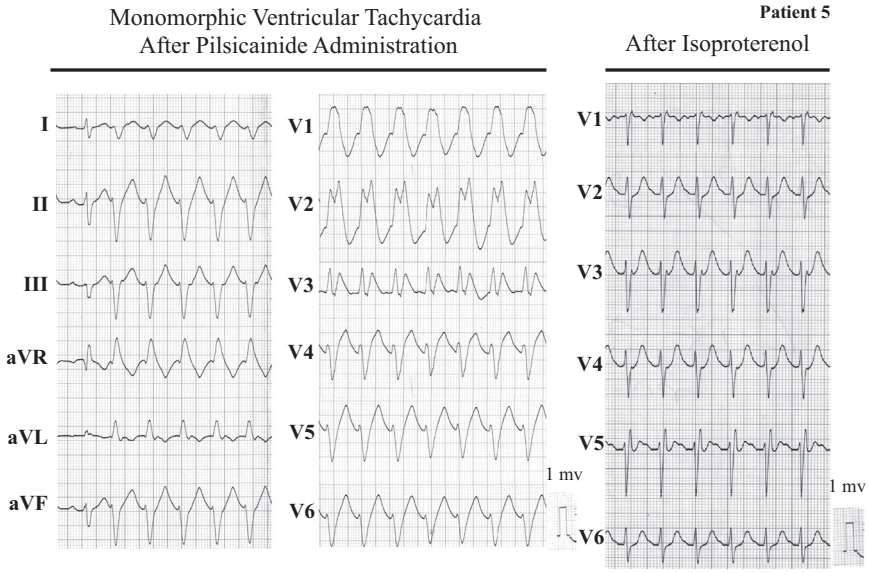

Fig. 5. Monomorphic ventricular tachycardia developed after pilsicainide administration in Patient 5 (left and middle panels). Normalization of ST-segment elevation in the right precordial leads was observed after infusion of isoproterenol.

leads V1 and V2 (type 3 Brugada ECG) (Fig. 4, left). A pilsicainide challenge test was performed, and the ECG changed to a type 1 Brugada pattern (Fig. 4, right), which was followed by monomorphic ventricular tachycardia (136 beats/minute) with a right bundle branch block pattern (Fig. 5, left). The ventricular tachycardia terminated spontaneously, and the STT changes in the right precordial leads resolved with intravenous infusion of isoproterenol (Fig. 5, right). A coronary angiogram indicated 90% stenosis of the proximal LAD (segment ♯7); thus, a stent was implanted (Fig. 2, lower panel). The patient refused electrophysiological study and ICD implantation. The exact mechanism of the ventricular tachycardia was unknown, but Ueyama et al. reported a similar case in which ventricular tachycardia originated from the left posterior fascicle [19].

Patients 2 and 3 were administered aspirin, and patients 1, 2, and 4 were administered dual antiplatelet therapy (aspirin + clopidogrel). The ECG pattern did not change significantly during follow-up Fig. 5.

3.6. *Follow-up*

No deaths occurred during the follow-up period. One patient without coronary artery disease suffered an arrhythmic event during follow-up for 4 months.

4. Discussion

In our patient series, coronary angiography was performed routinely prior to electrophysiological study, revealing a 9.1% (5/55) incidence of significant coronary artery stenosis in patients with Brugada syndrome/Brugada-type ECG. Although acute myocardial ischemia has been reported to cause right ventricular ST-segment changes similar to the Brugada-type ECG pattern [3–7] and coexistence of Brugada syndrome and vasospastic angina has been reported [8–12], only a few individual case

reports have suggested an association between significant coronary artery stenosis and Brugada syndrome [13–17]. Seow et al. [20] reported an interesting patient who presented with atypical chest pain, and the initial ECG showed a Brugada type 1 pattern. Subsequent ECGs depicted evolving anterior ST elevation myocardial infarction. The presence of a Brugada type 1 pattern masked the ECG changes indicative of acute anterior myocardial infarction, which made the diagnosis difficult. Hata et al. [21] described a patient who died suddenly due to VF documented by Holter monitoring, and a review of the patient's medical record revealed a Brugada type 2 ECG pattern. The autopsy revealed complete occlusion of the left main coronary artery. Ogano et al. [22] reported 2 asymptomatic patients with a saddleback Brugada-type ECG that dynamically converted to a coved-type pattern following ventricular arrhythmia episodes when myocardial ischemia occurred exclusively at the conus branch of the right coronary artery. These reports suggest that acute myocardial ischemia can mimic a Brugada-type ECG (and vice versa) and also that acute myocardial ischemia exacerbates the Brugada-type ECG pattern and has proarrhythmic effects. Therefore, coronary artery disease/ischemic heart disease should be considered when risk is being evaluated in patients with Brugada syndrome/Brugada-type ECG. According to the revised version of the "Guidelines for the primary prevention of ischemic heart disease" (JCS 2006 online only), the prevalence of ischemic heart disease in man was 8.13/1000 and 11.8/1000 in 2 cohort studies. It is very difficult to compare the prevalence of coronary artery disease between Brugada syndrome and non-Brugada syndrome because no data is available on the prevalence of coronary artery disease in the asymptomatic Japanese population, and many studies have indicated the annual incidence of ischemic heart disease in large cohort studies. As mentioned above, 2 studies have demonstrated the prevalence of coronary heart disease in Japanese men (8.13/1000 and 11.8/1000) [23,24]. In the present study, the incidence of coronary heart disease was 9.1%, which is almost 10 times higher than what was observed in previous studies. However, our study group included 2 patients with chest pain/oppression. Therefore, our results were slightly biased and could be merely coincidental. Unquestionably, age is related to risk, and remarkably, clinical, electrocardiographic, and electrophysiological characteristics were not statistically different in our patients with coronary artery disease compared to those without the disease.

4.1. Study limitations

In our patients, the Brugada-type ECG pattern did not change after coronary artery intervention or during follow-up under antiplatelet and antianginal drug therapies. Therefore, the relationship between Brugada syndrome and coronary artery disease was undefined. Additionally, the effects of ischemia on the Brugada-type ECG pattern and the effects of the Brugada-type ECG on the ischemia-induced ECG changes were not clarified.

5. Conclusion

We conclude that patients with a Brugada-type ECG should be evaluated for coronary artery disease. This is particularly true for patients in whom age could be a risk factor for the disease.

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